104 Antibiotic use in years preceding chronic lung infection with multiresistant *Pseudomonas aeruginosa*

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Intensive treatment of lung infection is standard CF care. We explored whether antibiotic (AB) use in *Pseudomonas aeruginosa* (*Pa*) colonized patients drives infection with multiresistant *Pa* (*MRPa*).
In 241 patients born after 1980 bacteriologic data plus AB use between 1995 and 2010 were analysed retrospectively. Chronic *Pa* infection was defined according to the Leeds criteria. *Pa* isolates resistant to all the AB of at least 2 classes were considered MR. Days on AB per year were counted in patients with chronic *Pa* infection who did and did not become infected with *MRPa*.
163 patients never acquired chronic *Pa* infection. 11 had chronic *MRPa* infection from onset, 35 had chronic *Pa* throughout, 32 had *MRPa* after chronic *Pa*. Yearly AB use during chronic *Pa* infection was analyzed in 25 subjects with chronic *Pa* and in 24 before onset of *MRPa*. Median days on IV AB per year was higher pre *MRPa* (43.2 days, IQR 30.0–62.4) than in patients never becoming *MRPa* (29.8 days, IQR 10.1–45.4), ($p = 0.05$). No difference was noted in use of oral AB (median 45.6 days IQR 24.4–68.7 vs 30.5 days IQR 20.5–124.9, $p = 0.54$) and inhaled AB (median 248.3 days IQR 168.5–365.0 vs 320.7 days IQR 208.5–353.7, $p = 0.45$). The proportion of patients who ever used azithromycin was not different (11/24 vs 7/25, $p = 0.15$). More patients with *MRPa* had siblings with CF (14/24 vs 3/25, $p = 0.02$). Median number of years of AB use, age and FEV_1 at last year of analysis were not significantly different.
A quarter of patients have *MRPa* from onset of chronic *Pa* infection. In the other *MRPa* subjects the yearly burden of AB use and having a sibling with CF were related to the development of *MRPa* infection.

105 Antibiotic dosing strategies of colistin on biofilm growing *Pseudomonas aeruginosa*: pharmacokinetic and pharmacodynamic issues

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The purpose of this study was to optimize the dosing strategies of colistin on the biofilm infections of *P. aeruginosa*. Killing curves of colistin on biofilms of non-mucoid and mucoid strains were made on Days 1, 3 and 7. The microtiter plate method was used to test minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) for planktonic bacteria, and the minimal biofilm inhibitory concentration (MBIC) and minimal biofilm eradication concentration (MBEC) were done on Days 1, 3 and 7. Pharmacokinetics (PK) and pharmacodynamics (PD) study was performed in a lung infection model of neutropenic mouse. Colistin showed concentration-dependent killing activity for biofilms of non-mucoid, and mucoid *P. aeruginosa* on Days 1, 3 and 7. The MBIC was 4–8-fold higher than the MIC, and the MBEC was 8–16-fold higher than the MBC of planktonic cells. The maximum bactericidal effect of colistin was attained at 2–12 h in biofilm-grown compared to 1–4 h in planktonic cells. MBIC and MBEC on Day 3 and Day 7 were higher than those on Day 1. The time of drug concentration exceeds MBEC (T>MBEC) was 0 when colistin was administrated systemically with the dose of 16 mg/kg. MBIC and MBEC of colistin were much higher than the MIC and MBC. The MBIC and MBEC of colistin increased with the age of the biofilm. Higher doses and longer treatment time of colistin were required for eradication of biofilm compared with the planktonic *P. aeruginosa*. The PK/PD indices of fAUC/MBIC and fAUC/MBEC are probably applied best for colistin in biofilms. Aggressive and early treatment of antibiotics and combined antibiotic therapy are highly recommended for biofilm eradication in CF patients.

106 Pharmacokinetic variability of clarithromycin is due to differences in CYP3A4 activity in patients with cystic fibrosis (CF) − a reason for treatment failure?

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Objectives: Clarithromycin (CLA) is used to treat CF patients and is metabolised in the liver by the enzyme CYP3A4. The Erythromycin Breath Test (ERMBT) measures CYP3A4 activity in vivo and may be used to identify patients needing larger doses of an antibiotic to avoid treatment failure. We investigated the correlation between CYP3A4 activity and the metabolism of CLA.
Methods: We included 22 CF patients (21–53 yr) with chronic lung infections. ERMBT: 0.15 MBq [14C-N-methyl] erythromycin i.v. were given. Every 10 min for 1 h the patients expired in a glass with 4 ml hyamine liquid collecting the exhaled CO_2. The ^{14}C activity was measured using liquid scintillation. 500 mg CLA was given orally and blood samples were collected every half hour for 3 h and at 6 and 12 h. The concentration of CLA and the metabolite 14-hydroxyCLA were measured by HPLC, and AUC, Tmax and Cmax were calculated.
Results: We found a 10-fold variation in AUC for CLA, median 881 ug/ml·min, a 12-fold variation in AUC for 14-hydroxyCLA median 366 ug/ml·min, a 16-fold variation in Cmax for CLA median 3.4 ug/ml and a 11-fold variation in Cmax for 14-hydroxyCLA median 0.9 ug/ml.
We found 8-fold variation in the CYP3A4 (ERMBT %14C/h), median 0.8. A linear correlation between the CYP3A4 activity and the metabolism of CLA expressed as the CLA/14-hydroxyCLA ratio was demonstrated ($P < 0.05$).
Conclusion: The large variation in the pharmacokinetic profile of CLA in CF patients may cause treatment failure. Similar problems may involve other antibiotics, which are metabolised by CYP3A4. ERMBT can be used to indentify CF patients who may be in risk of developing therapeutic failure or drug toxicity.

107 *In vitro* susceptibility of *Pseudomonas aeruginosa* (*PA*) does not predict clinical response to aztreonam 75 mg powder and solvent for nebuliser solution (AZLI): a responder analysis in subjects with cystic fibrosis (CF)

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Objective: Due to high achievable sputum concentrations of inhaled antibiotics, the utility of MICs to predict clinical response is not established. We conducted a retrospective responder analysis of CF subjects enrolled in a Phase 3 randomized trial of AZLI vs. tobramycin nebuliser solution (TNS) based on *PA* isolate susceptibility.
Methods: Data from subjects with CF and chronic *PA* infection treated with 3 intermittent 28-day courses of 75 mg AZLI (TID) or 300 mg TNS (BID) in a 6-month trial (ClinicalTrials.gov NCT00757237) were analyzed. Subjects were categorized by the MIC of their least susceptible *PA* isolate to aztreonam or tobramycin at the start of the 3rd course. Subjects were defined as improved if FEV_1 % predicted increased by ⩾6% or as worsened if FEV_1% predicted decreased by ⩾4% within the 3rd course. Data for subjects with no change is not presented.
Results: Comparing AZLI subjects with *PA* aztreonam MIC <128 mg/L vs. ⩾128 mg/L, 52% vs. 43% improved while 20% vs. 21% worsened, respectively. No differences were observed in AZLI subjects with *PA* aztreonam MIC <64 mg/L vs. ⩾64 mg/L; ~50% improved and ~20% worsened. Comparing TNS subjects with *PA* tobramycin MIC <16 mg/L vs. ⩾16 mg/L, 31% vs. 22% improved while 40% vs. 52% worsened, respectively. No differences were observed in TNS subjects with *PA* tobramycin MIC <4 mg/L vs. ⩾4 mg/L; ~30% improved and ~45% worsened.
Conclusions: *PA* susceptibility to either aztreonam or tobramycin was not predictive of clinical response in CF patients receiving multiple courses of therapy.
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